Multiexon deletion alleles of ATF6 linked to achromatopsia.

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Public Summary:
Achromatopsia (ACHM) is an autosomal recessive disease that results in severe visual loss. Symptoms of ACHM include impaired visual acuity, nystagmus, and photoaversion starting from infancy; furthermore, ACHM is associated with bilateral foveal hypoplasia and absent or severely reduced cone photoreceptor function on electroretinography. Here, we performed genetic sequencing in 3 patients from 2 families with ACHM, identifying and functionally characterizing 2 mutations in the activating transcription factor 6 (ATF6) gene. We identified a homozygous deletion covering exons 8-14 of the ATF6 gene from 2 siblings from the same family. In another patient from a different family, we identified a heterozygous deletion covering exons 2 and 3 of the ATF6 gene found in trans with a previously identified ATF6 c.970C>T (p.Arg324Cys) ACHM disease allele. Recombinant ATF6 proteins bearing these exon deletions showed markedly impaired transcriptional activity by qPCR and RNA-Seq analysis compared with WT-ATF6. Finally, RNAscope revealed that ATF6 and the related ATF6B transcripts were expressed in cones as well as in all retinal layers in normal human retina. Overall, our data identify loss-of-function ATF6 disease alleles that cause human foveal disease.

Scientific Abstract:
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